Annu. Rev. Public Health 2004. 25:155–97
doi: 10.1146/annurev.publhealth.25.101802.123020

HEALTH EFFECTS OF CHRONIC PESTICIDE EXPOSURE: Cancer and Neurotoxicity*[3]

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Key Words pesticides, epidemiology, exposure assessment, chronic disease, adult health

■ **Abstract** Pesticides are widely used in agricultural and other settings, resulting in continuing human exposure. Epidemiologic studies indicate that, despite premarket animal testing, current exposures are associated with risks to human health. In this review, we describe the routes of pesticide exposures occurring today, and summarize and evaluate the epidemiologic studies of pesticide-related carcinogenicity and neurotoxicity in adults. Better understanding of the patterns of exposure, the underlying variability within the human population, and the links between the animal toxicology data and human health effects will improve the evaluation of the risks to human health posed by pesticides. Improving epidemiology studies and integrating this information with toxicology data will allow the human health risks of pesticide exposure to be more accurately judged by public health policy makers.

[3]Abbreviations: AD, Alzheimer's disease; IARC, International Agency for Research on Cancer; USEPA, United States Environmental Protection Agency; JEM, job exposure matrix; NHL, non-Hodgkin's lymphoma; HCL, hairy cell leukemia; CLL, chronic lymphocytic leukemia; ALL, acute lymphoblastic leukemia; OPs, organophosphate insecticides; OPIDP, organophosphate-induced delayed polyneuropathy; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; CI, Confidence Interval [95% CI = 95% Confidence Interval]; OR, odds ratio; RR, relative risk; SMR, standard mortality ratio; DDT, 2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane.

INTRODUCTION

The widespread use of pesticides in agricultural settings, public health, commerce, and individual households throughout the world is an indication of the importance of these compounds (151–153). Yet, use of these chemicals entails exposure to the population from a variety of sources, including residues in food and water; applications to public spaces; home, garden, and lawn use; and, for some, occupational exposures (99, 105, 106). Given the widespread use of pesticides and the fact that we continue to find health effects associated with these chemicals, we need to be vigilant in postmarketing surveillance of the human health impacts (93, 98, 105).

To prevent public harm from exposures to pesticides, the USEPA and other regulatory bodies require premarket toxicologic testing in laboratory animals (93, 105, 230). However, the adequacy of this approach can be questioned because toxicologic testing is based on the relatively short-term administration of a single active ingredient to inbred strains of animals, whereas human exposures are to a complex mixture of compounds over a lifetime and human susceptibility varies in ways that are incompletely understood (75, 93, 230, 246, 278). While animal testing undoubtedly provides an excellent screening tool to keep many dangerous products off the market, the question remains: Do the products that pass these regulatory hurdles still affect human health?

Epidemiology studies continue to provide data to answer this question. Clearly, finding positive associations of disease with pesticide exposure in epidemiologic studies reflects limitations of current or past public health policy. If policy were completely effective, the only disease associated with pesticide use would be among those who accidentally or intentionally misuse the product; however, pesticide exposure affects more than this limited group. This suggests that current policies may not impart an adequate safeguard: Either animal testing alone or its interpretation in setting policy is not sufficient to protect public health.

Carcinogenicity and neurotoxicity reflect different mechanisms of toxicity, and different types of epidemiologic investigations are used to assess these effects. These two endpoints provide useful examples of the range of potential human health effects of pesticides, which are reviewed here. Limitations of space do not permit a discussion of additional pesticide-related health effects reported in the literature, but suggestions for future research and for public policy can be drawn from examining literature concerning these two relatively well-studied health outcomes. The major limitation of pesticide epidemiology historically has been inadequate exposure assessment. More accurate quantification of exposures has been the hallmark of some of the more recent epidemiological studies, and these advances are described.

HUMAN EXPOSURE TO PESTICIDES

Pesticides are a ubiquitous component of our environment. In 1999, over 1 billion pounds of pesticides were applied in the United States and over 5.6 billion pounds

were applied worldwide (99). Due to their widespread use in agriculture, schools, and homes, detectable levels of pesticides can be found in our homes and in our bodies.

Pesticides are defined as "substances used to prevent, destroy, repel or mitigate any pest ranging from insects, animals and weeds to microorganisms. . ." (99). Pesticides are commonly referred to by their functional class for the organisms that they are designed to control (e.g., herbicides, insecticides, or fungicides). Pesticides may also be grouped by their chemical class [e.g., organophosphate insecticides or triazine herbicides (see Table 1)]. In this case, pesticides, the "active ingredients," are combined with "other ingredients" to create the pesticide products on the market. "Other ingredients" include a wide array of compounds; information regarding some of these is considered confidential business information and is not publicly available. The health effects of a pesticide product may be a consequence of either the active ingredient or the other ingredients in the formulation or both.

Patterns of Pesticide Exposure

Individuals may be exposed to pesticides through both direct and indirect routes. Direct exposure occurs to individuals who personally apply pesticides in agricultural, occupational, or residential settings and is likely to result in the highest levels of exposure, whereas indirect exposures occur through drinking water, air, dust, and food and represent routes of long-term, generally low-level exposures. Indirect exposures may occur more frequently than direct pesticide application (106, 122, 260). Personal pesticide exposure in both occupational and residential settings is influenced by both the pesticide application characteristics and personal behavior. Spills and other unintended events also contribute to an individual's pesticide exposure (5, 7, 8). Over a decade ago, it was estimated that as many as 25 million agricultural workers worldwide experience unintentional pesticide poisoning each year (155). Not all spills result in overt poisoning episodes, but the impact of these events on total pesticide exposure, although hard to quantify, needs to be considered since they may represent the bulk of an individual's lifetime exposure to pesticides.

Epidemiologic Exposure Assessment Methods

Given the complexity of pesticide exposure, characterizing and appropriately assigning exposure in epidemiology studies is a challenge. In chronic disease studies, exposure assessment tools need to accurately characterize historic exposures. Detailed questionnaires and, to a lesser extent, biological markers have proved useful tools to assess long-term exposure.

Exposure assessment methods have progressed from crude surrogates, such as farming or living in a rural area, to identifying specific chemicals that may contribute to disease risk (Figure 1). Additionally, information on other factors that influence pesticide exposure, such as application methods and use of

TABLE 1 Commonly used pesticides, classified by type of pesticide and chemical class

Pesticide functional group	Chemical class	Examples*					
Herbicides	Phenoxy acetic acid	2,4-D	2,4,5-T	2,4,5-TP (Silvex)			
	Phenoxy benzoic acid	dicamba					
	Thiocarbamates**	EPTC	butylate	sulfallate			
	Triazines	simazine	atrazine	cyanazine			
	Anilides	alachlor	metolachlor				
	Dipyridyl compounds	paraquat	diquat				
	Phosphonates	glyphosate					
Insecticides	Organophosphates (OPs)	malathion	chlorpyrifos	parathion	diazinon	isofenphos	
	Organochlorines	DDT	aldrin	dieldrin	chlordane	lindane	heptachlor
	Carbamates	carbaryl	methomyl	carbofuran			
	Pyrethroids	permethrin					
	Rotenoids	rotenone					
Fungicides	Thiophthalimides	captan	captafol				
	Thiocarbamates*	metam sodium	ziram	thiram			
	Ethylene bis-dithiocarbamates (EBDCs)	maneb	zineb	mancozeb			
Fumigants		carbon tetrachloride					
		methyl bromide					
		sulfuryl fluoride					

*This table identifies pesticides referred to in the text and is not intended to be comprehensive.

**Thiocarbamates can be herbicides and fungicides.

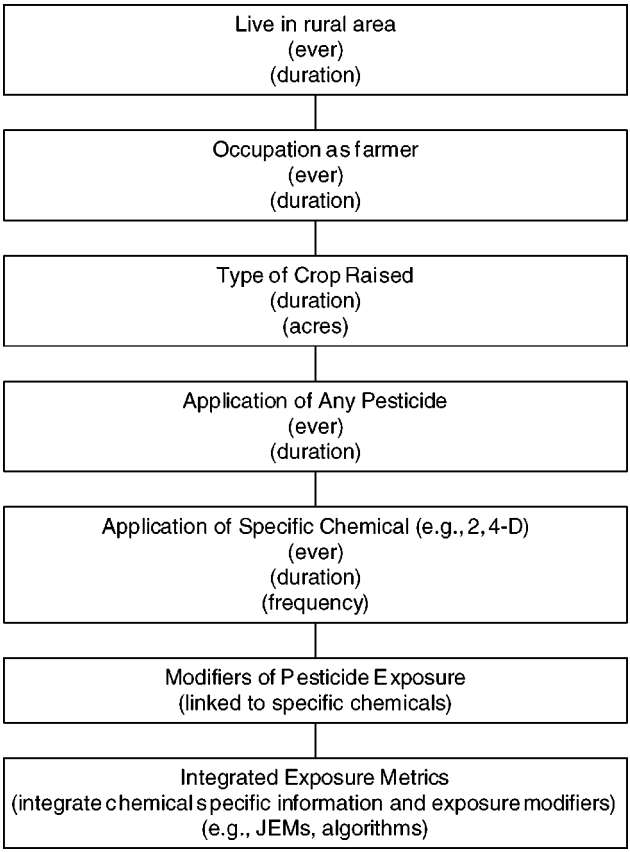

Figure 1 Evolution of exposure measures to assess occupational pesticide exposure.

personal protective equipment, can be collected to better estimate exposure. Exposure estimates can be further improved through the use of integrated metrics, such as exposure algorithms, job exposure matrices, and mapping techniques (discussed below). All pesticide exposure measures are clearly better when collected prospectively, that is, prior to disease onset, because most exposures do not leave "foot prints" indicating exposure duration and intensity and because time and disease can influence recall of exposures as well as interpretation of biological markers.

The primary goal of exposure estimation in epidemiology is to correctly rank individuals with regard to exposure level in the study population. To reduce exposure misclassification, it is critical to separate the nonexposed from the low and moderately exposed and to correctly identify the highly exposed individuals. To date, most of the focus on pesticide epidemiology has been in agricultural settings because the pesticide exposures are anticipated to be larger, and farmers can

provide better information regarding their pesticide exposure history than the general population because they buy and apply the chemicals themselves (33).

Questionnaires

Questionnaires have been used successfully to assess chronic pesticide exposure among farmers, farmworkers, and the general population. Farmers have been shown to provide reliable information regarding their personal pesticide use (31, 33, 91, 96, 146). Proxy respondents for farmers can report the functional classes of chemicals used (e.g., herbicides, insecticides) but are not as accurate with regard to individual pesticides (33). Investigators have used pesticide supplier reports (33) and repeated interviews (96) to assess the validity and reproducibility of reported pesticide use data. Overall, farmers appear to provide accurate exposure data with more reliable recall than some commonly used exposure measures, such as diet (31). Farmworkers, who are not farm owners or operators, often do not know what pesticides have been used on the crops on which they work but can accurately report crops worked and geographic region (95, 309). This information can be combined with other data regarding crop and pesticide usage to estimate potential pesticide exposures (274).

Questionnaires have also been used in chronic disease studies to assess residential pesticide use (47, 77, 121, 235, 280, 300). These questionnaires can be limited owing to inaccurate recall of personal pesticide use and exposure. Residents may not know what chemicals were used in their homes if professional applicators perform the pesticide application. These questionnaires have focused on identifying patterns of use and determining what type of pest was being treated (47, 77, 121, 235, 280, 300).

Biological Samples

The main exception to the use of questionnaires to assess long-term pesticide exposure has been the use of biological markers of organochlorine exposure. Organochlorine pesticides persist in adipose tissue for decades, making biological markers an appropriate tool to assess long-term exposure because recall of relevant exposures is difficult, if not impossible, for the general public. Collecting biologic samples prior to disease onset is critical because chronic diseases such as cancer may affect lipid metabolism and, thus, the significance of organochlorine concentrations among sick individuals (144, 232). For other chemical classes, long-lived biological markers are not available and, thus, questionnaires will continue to be the work horse of pesticide exposure estimation in large epidemiology studies.

Integrated Exposure Metrics

Integrated exposure metrics have been developed to enhance questionnaire information with data from other sources to better estimate pesticide exposure intensity.

These measures include job exposure matrices and exposure algorithms for occupational settings, and the use of geographical information systems (GIS) data for residential exposures. Factors such as application method, use of personal protective gear, work practices related to hygiene, as well as attitudes toward risk may all influence pesticide exposure and can be incorporated into exposure estimates.

Job exposure matrices (JEMs) have been employed to assess pesticide exposure in occupational settings, particularly in case-control studies (9, 156, 169, 184, 261, 284, 287, 305). JEMs incorporate information on job title, tasks, and industry to estimate exposure intensity in a population. Their efficiency and accuracy to correctly assign pesticide exposure history vary widely. Some JEMs use limited monitoring data to assign pesticide exposure based on job title and task, whereas others are based on region-specific job activities with exposure measurements collected among the populations studied. Specific agricultural JEMs have been developed for at least three different agricultural populations: South African farmworkers, rural Italians, and agricultural workers in British Columbia (184, 261, 305).

Exposure intensity algorithms are a natural extension of JEMs where the cumulative exposure to specific pesticides is weighted by chemical- and applicator-specific information in order to estimate exposure intensity and dose. Exposure intensity algorithms have the advantage of using the pesticide-specific information from the applicator, rather than assigning a pesticide exposure based on regional practices. For the Agricultural Health Study (AHS), Dosemeci and colleagues have developed algorithms that use measured exposure data to assign weights to determinants of exposure reported in questionnaires associated with pesticide application, work practices, and use of personal protective equipment (88). These exposure intensities are used to modify the reported lifetime cumulative pesticide application history for each chemical. Although the exposure algorithm of Dosemeci is designed for the multiple chemical exposures experienced by farmers and other pesticide applicators in large-scale studies, other investigators have developed chemical-specific algorithms in small-scale studies of a region or a specific agricultural group. Buchanan and colleagues developed a specific exposure algorithm to predict diazinon exposure among Scottish sheep dippers (43). Using measured exposure data to create simple surrogates of exposure that can be applied in large-scale studies via questionnaire is a critical aspect in improved exposure estimation for pesticide epidemiology studies.

Residential Exposure Estimates

Although the methods for pesticide exposure assessment are more refined for estimating occupational exposure, information collected from pesticide applicators is commonly used to estimate exposure to others in the population, both family members and rural residents (73, 106, 107, 122, 187, 203, 224, 267, 284, 300). Parental occupation and proximity of homes to treated fields has been used to assess organophosphate pesticide exposure among children (187). Use of geographic

information has been used to assess potential residential exposure to agricultural pesticides (23, 24, 61, 119, 120, 244). Use of mapping and remote-sensing data has allowed estimation of pesticide and other exposures from ground water and spray drift using data originally provided by pesticide applicators (293, 307). All these tools enhance the ability to assess pesticide health effects in agricultural communities, as well as other settings. Epidemiologic investigations have benefited from recent improvements in exposure assessment. Illustrations of this are presented in the cancer and neurologic disease sections that follow.

DO PESTICIDES CAUSE CANCER?

Some older pesticides including organochlorines (e.g., aldrin, chlordane, DDT, dieldrin), lead arsenate, creosote, and sulfallate are carcinogenic in animal studies (98, 152, 153, 225), and many of these pesticides continue to be used, particularly in developing countries (240). Pesticide formulations have also included carcinogenic solvents (98, 225). In humans, "occupational exposures in spraying and application of nonarsenical insecticides" as a group have been classified as probable human carcinogens (category 2A) by the IARC (153). However, epidemiologic studies relating pesticide exposure and human cancer have been inconsistent. Other than for arsenic, the epidemiological evidence regarding cancer probably cannot be considered to establish a causal relationship for any single pesticide at the present time (153). Although the weight of evidence suggests to IARC and others that occupational exposure to other insecticides is probably associated with human cancer (98, 153), the relationship is not considered causal because of the lack of high-quality evidence from epidemiologic studies of human cancer and the continuing uncertainties associated with extrapolating animal bioassay data to humans.

In this section, we review the epidemiological literature available for pesticide exposure and cancers. Owing to space limitations we do not present an exhaustive review but rather focus our attention on summarizing the evidence for select cancers where the literature, in our judgement, supports an association between pesticides and cancer (Table 2). For other cancers where the literature is less supportive of an association we simply summarize the literature at the end of Table 2. Childhood leukemias are discussed in this manuscript in the section on leukemias; for a discussion of other childhood cancers we refer the reader to other reviews (66, 159, 308, 312).

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) is among the most widely studied cancers in relation to pesticide use. In reviews of the literature, Blair & Zahm (32, 34) reported that NHL has been linked with phenoxyacetic acid herbicides, organochlorine pesticides, and organophosphate pesticides in analytical epidemiological studies.

In 18 of 29 studies, farmers were observed to show excesses of non-Hodgkin's lymphoma compared to the general population, but no excess was greater than twofold (32). Keller-Bryne et al.'s (164) meta-analysis of 6 studies examining the association between non-Hodgkin's lymphoma and farming in the central United States estimated the relative risk to be 1.34 (95% CI = 1.17, 1.55).

The literature linking specific pesticides to non-Hodgkin's lymphoma continues to grow, but the various studies do not yet offer a consistent etiological picture clearly identifying specific pesticides that may be responsible for the elevated risk observed. Population-based case-control studies have observed associations of NHL risk with self-reported agricultural exposures to specific organochlorine pesticides (53, 203, 306, 313). In a Canadian multicenter population-based incident, case-control study among men with a diversity of occupations, McDuffie et al. (203) found that among major chemical classes of pesticides, the risk of NHL was statistically increased with increased exposure to phenoxy and benzoic acid herbicides, and to carbamate and organophosphate insecticides, to amide fungicides, and to the fumigant carbon tetrachloride. In a pooled analysis of four population-based case-control studies in the Midwest, carbaryl, a carbamate insecticide, was found to be a risk factor for NHL (315). However, in a separate analysis of these same case-control studies, a significant association between organophosphate insecticides and NHL was limited to subjects with proxy respondents, casting doubt on the significance of the observed association (291).

In a U.S. population–based study of NHL conducted in five states and four metropolitan areas, Groves et al. (128) observed that differing demographic patterns and incidence trends occurred depending on the histologic type of NHL studied. They concluded that etiological studies should distinguish between histologic type in the analyses of these cancers (128).

Studies using biologic measures of organochlorine pesticides have been inconsistent. In a hospital-based, case-control study, Hardell et al. (136) found an NHL risk to be associated with serum chlordane and related compounds collected post-diagnostically, but in a population-based, case-control study using prediagnostic serum levels of several organochlorine compounds, Cantor et al. could not confirm this finding (55). The inconsistency between these two studies may point out the importance of using prediagnostic biological samples to establish etiological association whenever possible.

Fleming et al. (112) studied the mortality experience of pesticide-exposed workers across the United States using the 1986–1994 National Health Interview Survey. Compared to all other workers, farmers and pesticide applicators were at a greater risk of cancer mortality from the lymphatic-hematopopoietic cancers. Similar results were observed among female pesticide users in Iceland, but not among Icelandic men (316). In a small mortality study of those who manufactured or formulated 2,4-D no evidence of a link with NHL was reported (46).

The main exposures hypothesized to account for the observed associations are phenoxy acid herbicides and organochlorine insecticides. Dioxin [TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin)], a trace contaminant formed during the manufacture

TABLE 2 Summary of evidence linking pesticides to cancer

Cancer	Etiological evidence	Agricultural agents suspected	Selected references
Cancers frequently associated with pesticide exposures. (Literature supports a general association between pesticides and cancer)			
Non-Hodgkin's lymphoma	More than 30 studies in the literature. A majority of epidemiologic studies demonstrate an association between NHL and farming and/or pesticide application, but the relative risk estimates are generally less than 2. Looking for specific etiologic agents such as a pesticide or other farm exposures has produced inconsistent and therefore inconclusive results.	Phenoxyacetic acid herbicides, organochlorine insecticides, organophosphate insecticides, carbamate insecticides, dioxin contamination of pesticides, fumigants, fungicides, nitrates in drinking water in agricultural regions, solvents, zoonotic agents, dust	29, 32, 34, 42, 44, 46, 53, 55, 82, 90, 109, 112, 128, 133, 135, 162, 164, 197, 203, 221, 223, 277, 291, 292, 293, 306, 311, 313, 315, 316
Leukemia	More than 30 studies in the literature. A majority of epidemiologic studies demonstrate an association between leukemias and farming and/or pesticide exposure, but the relative risk estimates are generally less than 1.5. Looking for specific etiologic agents such as a pesticide or zoonotic viruses has produced inconsistent and therefore inconclusive results. Studies of specific leukemia subtypes are necessary. Studies of childhood leukemia suggest pesticide exposures indoors may be most important, as are exposures during critical time windows.	Insecticides: carbamates, organochlorines, organophosphates; herbicides; zoonotic viruses	32, 38, 39, 50, 57, 83, 135, 151, 173, 179, 192, 207, 215, 221, 241, 273

Multiple Myeloma	More than 30 studies in the literature. Majority of studies among both male and female farmers show an excess risk. Links to specific agricultural exposures are weak.	Infectious agents, solvents, pesticides	27, 29, 32, 35, 58, 165, 170, 177, 222, 227
Soft-tissue sarcoma	The epidemiological evidence supporting an association between herbicides and/or insecticides is inconsistent. The heterogeneous mix of soft-tissue sarcoma subtypes may explain the somewhat inconsistent pattern observed, or this may be a result of contaminants in some but not all pesticides being used.	Dioxin contaminants of several herbicides, herbicides, insecticides	2, 100, 132, 133, 141, 143, 190, 191, 238, 266, 290, 302, 306, 311
Prostate	More than 40 studies in the literature. A majority of epidemiologic studies demonstrate an association between prostate cancer and farming and/or pesticide exposure, but the relative risk estimates are generally less than 1.5. Evidence suggesting specific pesticide exposures is emerging but is in need of confirmation. Susceptibility genes may be involved in the prostate cancer-pesticide association.	Organochlorine insecticides, organophosphate insecticides, triazine herbicides, thiocarbamate herbicides, soil fumigants	1, 2, 4, 32, 49, 58, 81, 89, 111, 147, 163, 170, 210, 220, 262

(*Continued*)

TABLE 2 (*Continued*)

Cancer	Etiological evidence	Agricultural agents suspected	Selected references
Pancreas	More than a dozen studies in the literature. Pesticide use and pesticide manufacturing associated with increased risk in some, but not all studies.	DDT, fungicides	9, 11, 20, 32, 45, 54, 65, 102, 109, 114–116, 118, 155, 157, 196, 209, 219, 232, 233, 242, 250, 253, 265, 286, 304, 311, 316
Lung	Lung cancer is causally associated with exposure to arsenical compounds. The association with nonarsenical pesticides such as herbicides or herbicide contaminants is not as consistent. Smoking is an important cause of lung cancer, which hasn't always been controlled in these studies.	Arsenical compounds, phenoxy herbicides, phenoxy herbicide contaminants (i.e., dioxins and furans)	18, 21, 28, 37, 64, 98, 152, 188, 193, 194, 195, 218, 292
Ovary	Two case-control studies from Italy suggest an association of triazine herbicide use and ovarian cancer. A significant excess risk of ovarian cancer was observed in a U.S. cohort of pesticide applicators. The data available is insufficient to define a causal agent.	Triazine herbicides, pesticides	6, 84, 85, 86, 87, 97, 229, 263, 299

Cancers less frequently associated with pesticide exposures (literature less supportive of an association between pesticides and cancer)

Breast	The estrogenic activity of PCBs and DDE may contribute to increased risk of breast cancer. Recently, two cohort studies and five case-control studies show no convincing association.	DDT, DDE, PCBs, organochlorine insecticides	51, 70, 80 101, 117, 126, 130, 150, 161, 168, 186, 212, 214, 245, 276, 286, 288, 295, 303, 314
Testis	It has been suggested that the anti-androgenic activity of DDE and other organochlorinated insecticides may increase the risk of testicular cancer. A few studies of pesticide applicators have shown elevated risks of testicular cancer, but the data is inconsistent and no specific pesticides have been identified.	DDT, DDE, organochlorine insecticides	2, 28, 62, 92, 111, 211, 263, 277, 301
Hodgkin's disease	More than 30 studies in the literature. A small but significant excess risk is seen in a majority of studies of farmers. Specific etiologic agents have not been identified; evidence for any specific agricultural agent is weak.	DDT, insecticides, phenoxyacetic acid herbicides, infectious agents	58, 134, 141, 171, 175, 223, 311

(*Continued*)

TABLE 2 (*Continued*)

Cancer	Etiological evidence	Agricultural agents suspected	Selected references
Liver	Some evidence suggests that DDE levels in adipose tissue are associated with liver cancer in Whites but not among African Americans. Farmer laborers have elevated risk of liver cancer in some but not in most studies. Evidence is inconclusive.	DDT, DDE, pesticides	34, 63, 69, 113, 158, 183, 231, 271
Kidney	Associated with pesticides in two of four studies. No specific pesticides suggested as an etiologic agent. Evidence is inconclusive.	Pesticides	148, 198, 208, 256
Rectum	Elevated risk found in studies of pesticide users in Iceland and Italy; in pesticide manufacturers in Denmark, and farmers in Iowa (U.S.). Elevated risks are not generally found in farm populations, and no specific exposures have been hypothesized. Evidence is inconclusive.	Pesticides	58, 64, 114, 191, 218, 316

Brain and neurologic system	The great majority of cohort studies of pesticide manufacturing workers do not indicate an excess risk. Brain cancer was excessive among Missouri farmers and farmers in Italy and New Zealand, but not in Sweden. Higher levels of organochlorine compounds were found in adipose tissue of brain cancer patients than noncancer patients. Veterans exposed to herbicides during the Vietnam War were not at excess risk. Studies have not been able to identify specific pesticide associations. Evidence is inconclusive.	Insecticides, organochlorine insecticides, solvents, lubricating oil, phenolic compounds, polycyclic aromatic hydrocarbons, electromagnetic radiation	36, 41, 123, 159, 200, 205, 213, 239, 283, 308
Stomach	Herbicides applicators and manufacturers are associated with an excess risk in some but not all studies. Evidence is inconclusive.	Phenoxy acids, phenoxy acid contaminants (dioxin)	14, 29, 32, 140, 167, 264
Endometrium	Some evidence of an association. Few studies. Evidence is inconclusive.	Pesticides, organochlorine insecticides	126, 276, 296

of several chemicals including the phenoxyherbicides 2,4,5-T and 2-,4,5-TP [Silvex], has also been proposed to play a role in NHL etiology (166, 225). A role for other occupational and environmental exposures, including solvents, fuels, dust, zoonotic viruses, and nitrates in drinking water, has been suggested, but these alternative hypotheses have not yet been completely evaluated (30, 35, 42, 45, 90, 162, 197, 221, 292, 297). Since non-Hodgkin's lymphoma is a grouping of more than 20 phenotypes, future studies may benefit from more detailed assessment of risk by NHL phenotypes (128, 291).

Leukemia

Most studies of occupation and leukemia report an excess among farmers, but the excess is usually small (10% to 40%), and no clear pattern of risk for any histologic type has been observed (32). For more than 20 years, infection with zoonotic viruses has been proposed as a risk factor by a number of authors (83, 215, 221), but serologic confirmation of this has been lacking (50, 215, 221). Leukemia represents a vast array of hematopoetic malignancies including chronic and acute forms, which affect both children and adults. The etiologic evidence linking specific leukemia subtypes to pesticide use and other agricultural exposures is summarized below.

Chronic lymphocytic leukemia (CLL) was associated with the use of pesticides in a population-based, case-control study conducted in a farming and animal breeding area of northeastern Italy (215). The association of CLLs and working in farm-animal breeding may be partially explained by exposure to pesticides, particularly carbamates, organophosphates, and DDT. The independent effect of the childhood exposure suggests that early exposure, including possible contact with animals, may play a part in the pathogenic process of these neoplasms, possibly owing to viruses acting as oncogenic initiators or as immunosuppressors (215).

Hairy-cell leukemia (HCL) is a rare B-lymphoid chronic leukemia, which has only been investigated in a few epidemiologic studies. The specific definition of the disease makes it an interesting model for etiologic research on leukemia because its etiology may be less heterogenous than that of other more common groups of leukemia. A hospital-based study in France by Cavel et al. (57) found a significant association between organophosphate insecticide exposure and HCL risk. In a Swedish pooled multivariate analysis of two population-based, case-control studies of HCL and NHL, Hardell et al. observed a significant increased risk of the combined category of HCL and NHL for herbicides, but for no other category of pesticides (135). No clear etiologic picture has emerged yet for HCL.

The mechanism for the apparent association between certain leukemias and pesticide exposure is unknown. However, recent in vitro mechanistic studies may provide insight (38, 39, 173, 179, 273). Boros & Williams (39) recently reported that exposure of leukemic cell lines (K562) to increasing doses of an organophosphate

insecticide (isofenphos) resulted in dose-dependent leukemic cell proliferation. This mechanism may be common to other invasive tumors (38). In vitro data may not hold up in animals and humans studies, but exploration of this hypothesis in animal studies is necessary.

Ma et al. (192) examined household pesticide exposures among 162 childhood leukemias, primarily acute lymphoblastic leukemia (ALL), diagnosed between 1995 and 1999. Exposure information was ascertained by means of an in-home personal interview with the primary caregiver. Insecticide exposures early in life appeared to be more significant than later exposures, and the highest risk was observed for exposure during pregnancy, indicating the potential importance of timing of exposure. More frequent exposure to insecticides was associated with a higher risk, whereas exposure to herbicides was not. Exposure to indoor pesticides was also associated with excess leukemia risk, whereas outdoor use did not increase the child's risk of leukemia. A similar pattern of increased risk of childhood leukemia (specifically ALL) with maternal exposure to indoor pesticides was observed in a population-based study in Quebec, Canada (151). A large population-based study in Germany provided similar evidence for childhood lymphomas and leukemia (207). Reynolds et al. (241) analyzed data comparing population-based childhood (less than 15 years) cancer incidence rates throughout California to agricultural pesticide use during the period from 1988 to 1994. Overall no association was found between the amount of pesticide used in a census block and the childhood cancer incidence rates in the same census block. The same lack of association was seen for leukemia and central nervous system cancers. Indoor, not outdoor, exposure to insecticides is the most consistent risk factor identified for childhood leukemia.

In summary, a number of epidemiologic and environmental toxicology studies have provided evidence to support the etiologic association between insecticide exposures and leukemia, particularly childhood leukemia. However, the evidence supporting a link to any specific pesticide or class of pesticides is not strong.

Multiple Myeloma

Multiple myeloma, a common hematopoietic malignancy of plasma cells, has been gradually increasing in most parts of the world (74, 131). The pattern suggests an environmental etiology, possibly related to agriculture (29, 35, 222, 227).

Khuder et al. (165) conducted a meta-analysis of 32 peer-reviewed studies of multiple myeloma and farming, published between 1981 and 1996. An estimated relative risk among male farmers of 1.23 (95% CI 1.14–1.32) was observed; a similar risk was observed among female farmers (1.23) (171). Exposures proposed to be responsible for this elevated risk include infectious agents, solvents, and pesticides, but the evidence supporting an etiologic association with any of these exposures is not strong. Since the publication of Kruder's meta-analysis, at least two additional studies supporting a link between agricultural exposures and an elevated risk of multiple myeloma have been published (58, 177).

Soft-Tissue Sarcoma

Many (100, 132, 133, 290, 302), but not all, studies (141, 266, 306) have found an association between herbicide use and soft-tissue sarcoma. Two early Swedish case-control studies found particularly high risks [RR = 6.8 (95% CI 2.6–17.3)] (132), [RR = 3.3 (95% CI 1.4–8.1)] (133). Among Italian female rice weeders exposed to 2,4,5-T, an excess risk of soft-tissue sarcoma was observed [RR = 2.7 (95% CI 1.2–4.3)] (290). However, no significant risk was observed among those exposed to phenoxy herbicides in case-control studies in Kansas (141), New Zealand (266) or Washington state (306). The putative etiologic agent in most of these studies is dioxin (238).

Insecticide use has also been associated with soft-tissue sarcoma. In a population-based case-control study, the relative risk of soft-tissue sarcoma among Kansas farmers rose significantly with increasing time since first use. A relative risk of 4.9 was observed among those using insecticides on animals prior to 1946 (311).

The heterogeneous mix of cancer subtypes making up soft-tissue sarcoma may explain the somewhat inconsistent pattern observed (190). Studying all soft-tissue sarcoma combined may mask subtype-specific etiological associations. For example, Hoppin et al. observed that herbicide use was associated with malignant fibrohistiocytic sarcoma (OR = 2.9, 95% CI = 1.1–7.3) but not with liposarcoma (143).

Prostate Cancer

Prostate cancer risk among farmers and other pesticide users has been evaluated in over 40 studies in the United States and Europe (1, 4, 32, 49, 58, 62, 63, 81, 111, 147, 163, 170, 220). The relative risks are generally less than 2 (1, 32, 49, 58, 81, 89, 111, 163, 170, 220). Keller-Byrne et al. (163) estimated the relative risk to be 1.12 (95% CI 1.01–1.24) for the 24 studies evaluated in her meta-analysis. Until recently, however, no associations with specific pesticides or other agricultural chemicals were reported. In a hospital-based multi-site case-control study carried out in five rural areas of Italy, farmers exposed to organochlorine insecticides showed increased risk of prostate cancer, particularly for DDT (OR = 2.5, 95% CI 1.4–4.2) and dicofol (OR = 2.8, 95% CI 1.5–5.0) (262). Similar results were observed in a large, prospective cohort study of registered pesticide applicators in the United States where a pattern of chlorinated pesticide use was significantly associated with prostate cancer risk (4). In the latter study, use of methyl bromide, a widely used fumigant, was also associated with prostate cancer risk at the highest levels of cumulative lifetime exposure (4). Four organophosphate insecticides, a pyrethroid insecticide and a thiocarbamate herbicide showed a significantly increased risk of prostate cancer risk among study subjects with a family history of prostate cancer, but not among those with no family history (4). This study also found significant family history-by-pesticide interactions, possibly suggesting gene-environment interactions with selected pesticides (4).

A nested case-control study of prostate cancer was conducted within a large cohort of a predominantly Hispanic labor union in California, the United Farm Workers of America. By conducting an electronic record linkage between a roster of union members and the California Cancer Registry for the years 1988–1999, newly diagnosed cases of prostate cancer were identified within the union. Exposure to particular pesticides was inferred by linking employment records with employer's restricted-use pesticide records mandated by the State of California. Although risk was not associated with total pounds of pesticide applied, risk was increased with specific chemicals including lindane, heptachlor (both organochlorines) and simazine, and suggestive increases were observed with dichlorvos and methyl bromide (210).

Pancreatic Cancer

Pancreatic cancer risk was elevated in a number of occupational studies of agricultural workers and pesticide users including: farmers (102, 114, 209), licensed and unlicensed agricultural pesticide applicators (2, 9, 109, 116, 157, 219, 316), lawn care workers (310) and others exposed to pesticides (2, 54, 282). Garabrandt et al. observed a significantly elevated risk of pancreatic cancer among DDT manufacturing workers (OR = 4.8, 95% CI 1.3–17.6) (118). A recent study of outdoor workers in Australia showed a fivefold increased risk associated with DDT application (20). Six other studies of workers who manufactured pesticides, however, did not find a pancreatic cancer excess (11, 64, 118, 242, 253, 304), nor did four studies among farmers or farmworkers (35, 44, 115, 250).

In a population-based case-control study of pancreatic cancer in three areas of the United States, Ji et al. observed a modest but significant increased risk of pancreatic cancer associated with occupational exposure to fungicides (OR = 1.5, 95% CI 1.1–1.9) (156). In two case-control studies, postdiagnostic serum concentrations of DDE were significantly higher in pancreatic cancer cases than controls (144, 233). Two groups have examined the role of DDT and mutation of K-ras, a growth signal transduction gene that is commonly mutated in pancreatic cancer tumors (233, 265), but these studies were inconsistent.

Several methodologic challenges are inherent in the epidemiologic study of pancreatic cancer. Assessing exposures from personal interviews after disease onset is difficult because pancreatic cancer is quickly fatal. Pancreatic cancer is subject to diagnostic bias without histologic confirmation (118, 196, 234), and the impact of weight loss on the etiological interpretation of organochlorine pesticide metabolites in tissue must be considered (144, 285, 286). Ascertainment of exposure prior to disease is critical in order to study the role of pesticides in pancreatic cancer.

Lung Cancer

Lung cancer risk is causally associated with exposure to arsenical compounds (152), and an excess risk of lung cancer was observed among vineyard workers (188) and arsenical pesticide manufacturers (193, 194). A variety of other

pesticides have caused lung tumors in rodent bioassays, but the epidemiological data supporting an association for nonarsenical pesticides and lung cancer risk are mixed (98). In a study by Blair et al. (28) of licensed pesticide applicators in Florida the risk of lung cancer rose with the number of years licensed, with an SMR of 2.89 among those licensed for 20 years or more. In a survey of 1600 agricultural applicators in East Germany, Barthel (18) observed almost a twofold excess mortality from lung cancer. The risk increased to 3.0 among those with 20 or more years of exposure (18). The relationship between exposure to phenoxy herbicides and/or contaminants (dioxins and furans) was also observed for overall cancer and lung cancer mortality, specifically, among a cohort of workers from four manufacturing plants in Germany (21). Other studies of pesticide applicators (195, 292) and pesticide manufacturers (37, 65, 218) did not show any excess risk of lung cancer.

Ovarian Cancer

Two Italian case-control studies suggested a possible role in the etiology of ovarian cancer to the triazine herbicides, atrazine, simazine, and cyanazine, which are among the most frequently used agricultural herbicides in the United States. In the first, a hospital-based study, a relative risk of 4.4 for ovarian cancer was observed in women with "definite" or "probable" exposure to triazine herbicides (85). In a follow-up, population-based study the same authors reported a statistically significant relative risk of 2.7 for ovarian cancer among women exposed to triazine herbicides (87). In a prospective cohort of pesticide applicators and their spouses, a significant excess ovarian cancer risk (i.e., 8 observed, 1.9 expected) was observed among the female applicators but not among female spouses of the male applicators (6). The small number of cases made it impossible to identify the potential etiologic agent. Atrazine induces a variety of tumors in rats (229, 299) and mice of both sexes (84, 86). Atrazine and cyanazine are among the herbicides detected most frequently and at the highest concentrations in surface waters in the midwest corn belt of the United States (97).

Other Cancers

Several other cancers including cancer of the breast, testes, liver, kidney, rectum, and brain, and Hodgkin's disease have been tentatively associated with pesticide exposures on the farm or in pesticide manufacturing operations in some studies (Table 2). In the case of breast cancer, results of early studies could not be confirmed in later more rigorously designed studies. For Hodgkin's disease meta-analyses showed a small but significant excess risk among farmers. This may be a result of exposure to infectious microorganisms or pesticides used on the farm, but the association with either has been weak and inconsistent. The size of the literature is smaller for cancer of the testicles, liver, kidney, and brain and pesticides than for the other cancers cited, and the link with pesticides is weak and not sufficient at this time.

Comments

In summary, much of the epidemiology relating pesticides and cancer has suffered from inadequate assessment of exposure, and the validity of postdiagnostic collected biologic markers of exposure used in several studies has been called into question. For some cancer, e.g., soft-tissue sarcoma, leukemia, brain cancer, and non-Hodgkin's lymphoma, failure to account for potential etiologic differences between various histologic types of cancer may have masked important associations in previous studies. Currently, only arsenic-containing insecticides are recognized as carcinogenic in humans, although many others are suspected human carcinogens.

IS LOW-LEVEL PESTICIDE EXPOSURE NEUROTOXIC?

Pesticide exposure has profound effects on the nervous system. The consequences of high-level exposure are well established: Exposure is associated with a range of symptoms as well as deficits in neurobehavioral performance and abnormalities in nerve function. Whether chronic low-level exposure is neurotoxic is more controversial. Exposure to some pesticides may also be associated with increased risk of neurologic disease.

This section briefly summarizes what is known about the effects of high-level exposure and then considers in more detail the effects of low-level exposure on neurologic dysfunction and disease. Although pesticides may affect neurodevelopment among children, space considerations dictate that we restrict our attention to adults. Several types of neurologic endpoints are considered. Many studies have reported prevalence of a range of self-reported symptoms, often based on variations of an established checklist (189, 123). Mood and affect have also been assessed using self-report as well as validated scales. Neurobehavioral test batteries, including the WHO Neurobehavioral Core Test Battery (13), the Neurobehavioral Evaluation System (178), and portions of other batteries, have been used to evaluate cognitive and psychomotor function. These batteries have often been supplemented with tests of sensory and motor function. Other studies have investigated abnormalities in peripheral nerve conduction directly. Finally, there is a growing literature on specific neurologic diseases.

High-Level Exposure

Neurotoxicity can result from high-level exposure to most types of pesticides, including organophosphates (OPs), carbamates, organochlorines, fungicides, and fumigants (160), but only OPs have been studied in detail (138, 160). The immediate response to OPs can occur within minutes. Mild cases display symptoms including headache, dizziness, nausea, vomiting, pupillary constriction, and excessive sweating, tearing, and salivation. More severe cases develop muscle weakness and muscle twitches, changes in heart rate, and bronchospasm and can progress to

convulsions and coma. These symptoms are a consequence of overstimulation of postsynaptic cholinergic receptors following inhibition of acetylcholinesterase by OPs. An intermediate syndrome, occurring one to four days after exposure, is characterized by muscle weakness and can be fatal if respiratory muscles are affected. Two to five weeks after exposure, some patients develop organophosphate-induced delayed polyneuropathy (OPIDP), a well-characterized syndrome involving sensory abnormalities, muscle cramps, weakness, and even paralysis, primarily in the legs. These symptoms are a consequence of axonal death following OP inhibition of a neural enzyme called neuropathy target esterase and may be irreversible.

Several studies have shown that OP poisoning has long-term sequelae in addition to OPIDP. Studies of individuals with a history of pesticide poisoning, either farmworkers (182, 201, 217, 275) or from the general population (254, 270), have found that increased symptom prevalence, deficits in cognitive and psychomotor function, decreased vibration sensitivity, and impaired nerve conduction can occur long after the immediate episode is resolved. In some cases effects were observed 10 or more years after poisoning (254), which suggests that the residual damage is permanent. Even mild poisoning can have long-term consequences: Banana farmworkers who had been treated for intoxication with OPs or carbamates but did not require hospitalization performed worse on tests of cognitive and psychomotor function, compared to nonpoisoned workers (298).

Chronic Low-Level Exposure

SYMPTOM PREVALENCE Even in the absence of poisoning, chronic exposure is associated with a broad range of nonspecific symptoms, including headache, dizziness, fatigue, weakness, nausea, chest tightness, difficulty breathing, insomnia, confusion, and difficulty concentrating. Farmworkers exposed to multiple pesticides (124) and nursery workers exposed to OPs (19) reported increased symptom prevalence compared to unexposed workers. Farmers and farmworkers (184, 217, 275), commercial termiticide applicators (269) and sheep dippers (228) who applied OPs all had higher symptom prevalence than nonapplicators. Increased symptom prevalance was associated with depressed acetylcholinesterase levels in two studies of farmworkers (124, 217). Another study found that increased symptom prevalance was associated with self-reported pesticide exposure but not with depressed acetylcholinesterase levels (60). Although recall bias may explain this finding, it is also possible that pesticides other than OPs affect symptom prevalence. For example, exposure to DDT (289) and fumigants (12) has been associated with increased symptom prevalence.

MOOD AND AFFECT Pesticide exposure is also associated with changes in mood and affect. Workers exposed to OPs (19, 269) or DDT (289) reported higher levels of tension, anger, and depression. Farmers who applied pesticides reported more tension during the application season than off-season (275), but this is not necessarily related to pesticide use. Farmers who reported a history of

pesticide-related illness were more likely to score high on a depression scale (CES-D) than those who did not (268). However, other studies of exposure to OPs (10) or fumigants (52) were negative.

NEUROBEHAVIORAL PERFORMANCE Most studies indicate that pesticide exposure is associated with deficits in cognitive function. Sheep dippers (272) and nursery workers (19) exposed to OPs, malaria-control workers who sprayed DDT (289), vineyard workers exposed to fungicides (15), fumigators exposed to sulfuryl fluoride but not methyl bromide (12, 52), and farmers (68), farmworkers (124), and pesticide applicators (104) exposed to multiple pesticides all showed worse performance on tests of cognitive function. It is important to note that these studies are not fully consistent. Most studies found deficits on one or several tests of cognitive function, but not on other tests, and there was not full agreement among studies in which tests were affected. Further, no deficits in cognitive function were found in other studies of OP exposure (10, 76, 108, 269).

Pesticide exposure is also associated with deficits in psychomotor function. Farmworkers (76, 124, 182) and termiticide applicators (269) exposed to OPs, malaria-control workers who sprayed DDT (289), vineyard workers exposed to fungicides (15), and fumigators exposed to methyl bromide or sulfuryl fluoride (12, 52) showed worse performance on tests of psychomotor function. Again, results on individual tests were not fully consistent within or among studies, and no change in psychomotor function was evident in other studies of OP exposure (10, 68, 108).

SENSORY AND MOTOR FUNCTION Neurobehavioral test batteries are often supplemented with tests of sensory or motor function. One frequently used test is vibration sensitivity, which evaluates peripheral somatosensory function. Most evidence suggests this is not affected by low-level exposure. One study found decreased sensitivity (275), and another found both decreased sensitivity and other signs of peripheral neuropathy (67), but other studies of individuals exposed to OPs (182, 185, 228, 269), DDT (297), or fumigants (12) found no change. Data on other aspects of sensory function are limited. Very few studies have considered motor function: Neither tremor (185, 269) nor grip strength (12, 289) was related to pesticide exposure. Balance is commonly evaluated by a test of postural sway. Two studies of applicators exposed to OPs (269) or to multiple pesticides (249) found deficits in balance, although results from another study of OPs were negative (10).

NERVE CONDUCTION Studies that have evaluated peripheral nerve conduction have produced largely negative results. Several studies of OP exposure found little evidence of impaired nerve conduction (10, 94, 269). One study of fumigators found deficits in nerve conduction (52), but another did not (12). In contrast, fungicide exposure was related to impaired nerve conduction in a study of bulb farmers, which also found deficits in autonomic nerve function (248).

Comment Overall, these studies suggest that the central nervous system may be more vulnerable to pesticides than the peripheral nervous system. However, the data are sparse and inconsistent and do not yet support firm conclusions (247). Some of the inconsistencies among these studies are likely due to methodologic differences.

A critical issue is exposure. Qualitative and quantitative aspects of the exposure under consideration differed among studies, as did the ability of the studies to assess exposure. Exposure metrics ranged from job title to detailed assessment based on work history and job-exposure matrices; biomarker data were occasionally available. Although many studies collected information on duration or other aspects of exposure, more than half of them based their primary analysis on a comparison of exposed and unexposed groups defined a priori. There is, however, no clear-cut relationship between the quality of exposure assessment and the results of the studies. On the other hand, some of the studies that found no association of pesticide exposure with neurologic function clearly involved very low and well-controlled exposures, for example, well-trained pesticide applicators working under careful supervision and using personal protective equipment. Further, the choice of comparison group may influence results. Some studies have used as referents individuals from the same community or workplace as the exposed participants. Although the former may have no documented exposure, they may nevertheless not be truly unexposed, again limiting the power of the studies to detect effects.

Neurologic Disease

PARKINSON'S DISEASE There is an extensive literature suggesting that pesticide exposure may increase risk of Parkinson's disease (PD) (142, 174, 176, 237, 281). Many studies have found that PD risk is related to living in rural areas, drinking well water, and farming as an occupation (237). More specifically, numerous case-control studies have observed that pesticide exposure is associated with increased PD risk. Studies published prior to 1999 were reviewed by Le Couteur et al. (176), who noted that 12 of 20 studies found a positive association, with odds ratios ranging from 1.6 to 7.0. In many of the studies, exposure was defined as ever exposure to any pesticide. This broad definition permits significant misclassification, which might minimize the association. In the time since this review, only one of five case-control studies published has found a relationship of pesticide exposure to PD risk (22, 103, 172, 279, 236), but definition of exposure in these later studies was similarly broad. In contrast, two recent cohort studies with prospectively collected exposure information have provided support for the hypothesis. PD risk was related to years of plantation work and to self-reported pesticide exposure in men enrolled in the Honolulu Heart Program cohort (226). Occupational exposure to pesticides assessed with a job-exposure matrix was strongly associated with PD risk (odds ratio 5.6) in an older cohort living in a vineyard-growing region of France (16).

Only a few studies of pesticide exposure and PD risk have been able to implicate specific pesticides. Several studies found increased risk associated with

exposure to either insecticides or herbicides (48, 125, 259), and one study indicated that risk was elevated by exposure to organochlorines, organophosphates, or carbamates (258). Several studies have implicated paraquat (139, 181). This compound is of great interest because of its structural similarity to MPTP, a contaminant of synthetic heroin observed in the early 1980s to produce a parkinsonian syndrome in recreational drug users and subsequently used to investigate mechanisms involved in the etiology of PD (174). In addition to analytic studies, several case reports have described PD in individuals exposed to organophosphates (26, 78), glyphosate (17), paraquat (251), diquat (257), maneb (206), and other ethylene bis-dithiocarbamates (142). Higher concentrations of organochlorine residues, particularly dieldrin, have been found in postmortem brains of PD patients compared to patients with other neurological diseases (71, 110). Animal models have also implicated specific pesticides in the etiology of PD, including rotenone, paraquat, and maneb (25, 281).

OTHER NEUROLOGIC DISEASE Information on pesticide exposure and other neurologic diseases is more sparse. Several studies have suggested that risk of amyotrophic lateral sclerosis (ALS) is related to farming as an occupation although not necessarily to living in rural areas (216). Pesticide exposure has been considered in six case-control studies; three found some evidence for an association (79, 204, 255), whereas three others found none (59, 127, 129). Only one study presented detailed exposure information (204): Based on an industrial hygiene assessment of a complete occupational history, pesticide exposure was associated with a more than twofold increase in ALS risk, with greater risk at higher levels of exposure.

Dementia has also been related to pesticide exposure. Occupational pesticide exposure was associated with Alzheimer's disease (AD) risk in a large population-based, case-control study (202), although another smaller study of environmental exposure to the general population found no relationship (121). Occupational exposure to pesticides assessed with a job-exposure matrix was associated with a twofold increase in risk of AD in a cohort of older individuals living in a vineyard-growing region of France (16). Occupational pesticide exposure was also associated with vascular dementia (180) and with risk of dementia among PD patients (149). Pesticide exposure was associated with mild cognitive dysfunction in a prospective cohort study of cognitive aging (40). It is important to realize, however, that the basic neurochemical defect in AD is loss of cholinergic neurons, and that to increase cholinergic tone, AD is sometimes treated with organophosphate cholinesterase inhibitors (243).

DISCUSSION

Epidemiologic evidence clearly suggests that at current exposures pesticides adversely affect human health. Thus, human studies on exposure and health effects complement the current process of regulation based on animal toxicity testing.

Extrapolation from animals to humans may not always be appropriate because pesticide metabolism may differ in animals and humans. Further, human exposure may be intermittent, may occur through a variety of routes (e.g., dermal, oral, inhalation), and may be to a complex formulation, in contrast to continuous oral exposures to single chemicals in animals. Epidemiology studies are crucial because they provide data on the relevant species, relevant diseases (not animal models of human disease), and the relevant exposures. The remaining challenge is to more fully integrate information from human studies into regulatory and public policy processes in order to minimize the health impacts of pesticides.

Three approaches can contribute to this process: further research on human health effects of pesticides, increased surveillance of pesticide poisoning, and exposure monitoring. Information on human health effects is obviously not available for new chemicals prior to their release on the market. However, data regarding health effects of related chemicals can inform regulatory decisions. Additionally, health effects information can be available at the time a pesticide is reregistered. Increased surveillance of pesticide poisoning will also help to identify specific chemicals or exposure circumstances in need of further regulation. Equally important is identifying a strategy to ensure that risk assessment assumptions regarding levels of exposure in the population are accurate. There is evidence to suggest that environmental exposures are exceeding these levels. In 2003, Castorina and colleagues (56) reported that up to 35% of pregnant women in a farming region of California had levels of urinary organophosphate metabolites that exceeded the USEPA margin of exposure for total organophosphates. Exposure monitoring studies are thus crucial to our knowledge of the impact of pesticides on human health and to the control of these exposures.

The value of further epidemiologic research to public health will depend at least in part on use of improved methodology, for both study design and exposure assessment. Prospective cohort studies have several important advantages compared to other study designs, yet they require large populations with long follow-up periods to study cancer or other chronic diseases. Many existing studies, particularly those conducted within manufacturing facilities of a few hundred workers, will never have the statistical ability to identify cancer risks to specific chemicals unless the risk is very large, and null results from these studies should not be interpreted as evidence that a pesticide poses no risk to human health. Further, cause-specific mortality is often used to identify pesticide-related risks in studies based in occupational settings. Although this approach is clearly important, it is not useful for diseases with a low case-fatality rate and may thus underestimate the impact of exposure on disease. Studies of disease incidence will better estimate the impact of pesticide-related morbidity. Case-control studies are critical for studying rare diseases and can provide the opportunity to collect confounder information or biological samples in a cost-efficient manner. Case-control studies nested in cohort studies with prospectively collected exposure information combine the best of both approaches.

Continued focus on improving exposure assessment techniques for health effect studies will advance our understanding of the impact of pesticides on human

health. Epidemiology studies benefit when patterns and duration of exposure can be quantified and when questionnaire-based exposure metrics can be validated in laboratory and field studies. Collecting exposure data and data on potential confounders prospectively, prior to disease occurrence, is preferable to retrospective ascertainment because the latter approach is prone to errors in recall. If these errors are influenced by disease status, bias can be introduced. Prospective cohort studies are expensive and time consuming, particularly for rare diseases. Retrospective exposure metrics need to be improved to minimize the impact of recall bias because case-control studies will continue to provide key information on the role of pesticides in rare disease.

Because pesticide applicators frequently use a range of chemicals over their lifetime, identifying specific agents associated with disease is challenging. However, by understanding various aspects of exposure, including patterns of use, factors affecting individual exposure, and the other ingredients in the pesticide product, researchers will be better equipped to evaluate whether health effects associated with use of a particular pesticide are related to a specific pesticide product, exposure to a class of chemicals with a similar mechanism of action, interaction of chemical mixtures, or the other ingredients in the formulation. Because humans are exposed to a vast array of chemicals on a daily basis, the reductionist approach used by toxicology, testing one chemical at a time, may be an incomplete strategy to assess the true human health impact of exposure.

Genetic variation influences human susceptibility to pesticides. For example, metabolism of OPs is influenced by a number of genes including paraoxonase (PON1) and the cytochrome P450s (69, 72, 75, 113, 161, 278). Recently, polymorphisms in PON1 were associated with increased prostate cancer risk among Finnish men (199). Whether pesticide exposure and these genes contribute to prostate cancer is not yet known, but the role of genetic variation in pesticide toxicity is a new and promising area of research that needs further attention.

Animal toxicology studies could help identify potential biomarkers of exposure or early effects. Application of these in human studies could also identify and quantify sources of variability in human response. Studies of exposed individuals utilizing biological markers to assess exposure and short-term measures of effect might also facilitate understanding of the concordance or lack thereof between animal models and human health effects.

Given their importance in agriculture, vector control, and structural protection, pesticides will continue to be used and will therefore be present in the human environment. Epidemiologic studies of cancer and neurologic disease suggest that human health effects occur at current exposure levels in occupational and environmental settings. Better understanding of the patterns of exposure, the underlying variability within the human population, and the links between the animal toxicology data and human health effects will allow better evaluation of the risks to human health posed by pesticides. Improving epidemiology studies and integrating this information with the existing toxicology data will allow the human health risks of pesticide exposure to be more accurately judged by makers of public health policy.

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